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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

MAIL DATE	DELIVERY MODE
05/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,964	BAM ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-20,22-38 and 40-47* is/are pending in the application.

4a) Of the above claim(s) *2-5,23-28,30-35 and 43* is/are withdrawn from consideration.

5)☒ Claim(s) *9-20,29,37,38,42,45 and 47* is/are allowed.

6)☒ Claim(s) *1,22,36,41,44,46* is/are rejected.

7)☒ Claim(s) *6 and 40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/20/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicants Response and Amendments filed 20 February 2007 are acknowledged. Applicant's amendments to the claims are entered. Applicant's amendments to the specification are NOT entered for the reasons set forth below.

Formal Matters

2. Claims 1-6, 9-20, 22-38, and 40-47 are pending. Claims 7-8, 21, and 39 have been cancelled by Applicant. Claims 2-5, 23-28, 30-35, and 43 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 1, 6, 9-20, 22,29, 36-38, 40-42, and 44-47 are under examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 20 February 2007 has been considered to the extent possible. The reference to the International Search Report fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The references contained within the International Search Report has been considered insofar as they have been cited by the Examiner (EP 0845530 A2) or listed elsewhere in the IDS (Francis et al.,). A signed copy is attached hereto.

Specification - Objection

4. The objection to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code (p. 7, line 4) is maintained for the reasons of record. It is noted that Applicant's have submitted an Amendment to the Specification (filed 20 February 2007) to correct the hyperlink. However, Applicant has not used the proper markings to show what text has been deleted. See 37 CFR 1.530(d)(1), which states that [c]hanges to the specification, other than to the claims, must be made by submission of the entire text of an added or rewritten paragraph including markings pursuant to paragraph

(f) of this section, except that an entire paragraph may be deleted by a statement deleting the paragraph, without presentation of the text of the paragraph. The precise point in the specification must be identified where any added or rewritten paragraph is located. This paragraph applies whether the amendment is submitted on paper or compact disc (see §§ 1.96 and 1.825). The objection may be overcome by enclosing the text to be omitted in brackets.

Claim Objections

5. The objection claims 21 and 22 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is withdrawn in light of Applicant's amendments.

6. Rejections of claims 7-8, 21, and 39 are withdrawn as being moot in light of Applicant's cancellation of the claims.

7. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. Claim 40 is objected to as being a substantial duplicate of claim 29. Claim 40 is drawn to a product-by-process. Patentability of a product-by-process claims is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it (*In re Thorpe* 227 USPQ 964 (Fed. Cir. 1985)) (see also, MPEP § 2113).

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. The rejection of claims 9-20, 22, 29, 37-38, 41-42, and 44-47 under 35 U.S.C. 112, first paragraph, are withdrawn in light of Applicant's amendments.

Claim Rejections - 35 USC § 112, Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. The rejection of claims 9-10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in light of Applicant's claims.

13. The rejection of claim 1 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in light of Applicant's amendment.

14. The rejection of claim 6 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in light of Applicant's amendment.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Yamamoto et al., EP 0845530 A3 (published 3 June 1998) (see especially, SEQ ID NO: 7 and claim 5) (cited in the Office Action of 17 October 2006), is maintained for the reasons of record and the reasons set forth herein.

Applicant argues that the claim has been amended to recite "said substitution being from three to five amino acid residues" and that Yamamoto et al., do not teach a human IL-18 substitution mutants

comprising from three to five amino acid substitutions in the sequence of SEQ ID NO: 1. Applicant's argument has been fully considered, but is not persuasive.

Claim 1, of the claim set filed 20 February 2007, has not been amended in the form Applicant suggests on page 10, last paragraph of Applicant's Remarks, filed 20 February 2007. The claim still states "said substitution being from one to five amino acid residues." For purposes of compact prosecution, the Amendment suggested by Applicant of "said substitution being from three to five amino acid residues" would place the EP 0845530 (Yamamoto et al.) reference outside the scope of the claims, as amended. However, the current claims under examination, only require "said substitution being from one to five amino acid residues." As such, the EP 0845530 reference is still applicable, as it anticipates instant claim 1, as written.

17. The rejection of claims 36, 41 and 44 under 35 U.S.C. 102(e) as being anticipated by Burton et al., US PreGrant Publication US 2004/0136992 (15 July 2004, benefit to 28 August 2002), are withdrawn in light of Applicant's amendments.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of

each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. The rejection of claims 36-38 and 40 under 35 U.S.C. 103(a) as being unpatentable over Burton et al., US PreGrant Publication US 2004/0136992 (15 July 2004, benefit to 28 August 2002) in view of Martinez et al., US PreGrant Publication US 2004/0062746 A1 (1 April 2004, benefit to 12 December 2002) in further view of Benjamin et al., (Ann Rev Immune 1984 2:67-101), is withdrawn in light of Applicant's amendments.

22. The rejection of claims 41-42, 44-45, and 46-47 under 35 U.S.C. 103(a) as being unpatentable over Burton et al., US PreGrant Publication US 2004/0136992 (15 July 2004, benefit to 28 August 2002) in view of Martinez et al., US PreGrant Publication US 2004/0062746 A1 (1 April 2004, benefit to 12 December 2002) in further view of Kim et al., (J Biol Chem 29 March 2992; 277(13):10998-11003), is withdrawn in light of Applicant's amendments.

New Claim Rejections Under 35 USC § 103 – Necessitated by Amendment

23. Claims 22 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burton et al., US PreGrant Publication US 2004/0136992 (15 July 2004, benefit to 28 August 2002) (cited in the Office Action of 17 October 2006) and Janson et al., US Pregrant Publication US2003/0232032 (18 December 2003, benefit to 17 April 2002), in view of Cox et al., (US Patent 6,753,165, 22 June 2004, benefit to 6 September 2001).

The claims are drawn to human wild-type IL-18 polypeptide and method for making the same, wherein the polypeptide is conjugated to a water-soluble polymer (PEG moiety) at the cysteine at residue 38 and the cysteine at residue 68.

Burton et al., teach a composition and a method of preparing a biologically active composition comprising human IL-18 and covalent derivatives prepared by linking chemical moieties, such as polyethylene glycol, to functional groups (paragraph 143). Increased pharmacokinetics and bioavailability are taught at paragraphs 143-146. Compositions administered by injection and transdermally are taught at paragraph 221. Covalent derivatives are taught at paragraph 143. IL-18 amino acid substitution mutants, including cysteine mutants and inactivation of N-glycosylation sites, are taught at paragraph 143. Burton et al., do not teach pegylation at cysteine 38 or cysteine 68.

Janson et al., teach the crystal structure of human and murine IL-18 with cysteine-38 and cysteine-68 as being free, solvent accessible cysteine residues (especially Table 1, pp. 8 and 12).

Cox et al., (US Patent 6,735,165, 22 June 2004, benefit to 6 September 2001) teach covalent modification of proteins with polyethylene glycol (PEG) by covalently attaching a PEG moiety to a cysteine residue using cysteine-reactive PEGs (column 3, lines 1-62). A number of highly specific, cysteine-reactive PEGs with different reactive groups (e.g., maleimide, vinylsulfone) and different size PEGs (2-40 kDa) are commercially available. At neutral pH, these PEG reagents selectively attach to "free" cysteine residues, i.e., cysteine residues not involved in disulfide bonds. Cox et al., also teach that covalent modification of proteins with polyethylene glycol (PEG) has proven to be a useful method to extend the circulating half-lives of proteins in the body (column 1, lines 38-65). Covalent attachment of PEGs to a protein increases the protein's effective size and reduces its rate of clearance from the body. PEGs are commercially available in several sizes, allowing the circulating half-lives of PEG-modified proteins to be tailored for individual indications through use of different size PEGs. Other documented *in vivo* benefits of PEG modification are an increase in protein solubility, stability (possibly due to protection of the protein from proteases) and a decease in protein immunogenicity.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Burton et al., with the teachings of Janson et al., and Cox et al., because Burton et al., teach that IL-18 derivatives can be conjugated with polymer moieties, Janson et al., teach the crystal structure of IL-18 with cysteine-38 and cysteine-68 as being solvent accessible, and Cox et al., teach cysteine-reactive PEG moieties of various sizes. The person of ordinary skill in the art would have been motivated to PEGylate cysteine-38 and cysteine-68 because Cox et al., also teaches that covalent modification of proteins with polyethylene glycol (PEG) has proven to be a useful method to extend the circulating half-lives of proteins in the body (column 1, lines 38-65). Covalent attachment of PEGs to a protein increases the protein's effective size and reduces its rate of clearance from the body. PEGs are commercially available in several sizes, allowing the circulating half-lives of PEG-modified proteins to be tailored for individual indications through use of different size PEGs. Cox et al., also teach other benefits of PEG modifications including an increase in protein solubility, stability (possibly due to protection of the protein from proteases) and a decease in protein immunogenicity. The person of ordinary skill in the art would have reasonably expected success because Cox et al., teach the method by which free, solvent accessible cysteine residues may be pegylated and Janson et al., confirm by crystal structure, that cysteine-38 and cysteine-68 of human IL-18 are freely available and are solvent-accessible.

24. Claims 41, 44, 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burton et al., US PreGrant Publication US 2004/0136992 (15 July 2004, benefit to 28 August 2002) (cited in the Office Action of 17 October 2006) and Janson et al., US Pregrant Publication US2003/0232032 (18 December 2003, benefit to 17 April 2002), in view of Cox et al., (US Patent 6,753,165, 22 June 2004, benefit to 6 September 2001), in further view of Kim et al., (J Biol Chem 29 March 2992; 277(13):10998-11003) (cited in the Office Action of 17 October 2006).

Burton et al., Janson et al., and Cox et al., teach as stated, *supra.*

Kim et al., teach that IL-18 binds and neutralizes IL-18BP biological activity (p. 10998, column 2, third paragraph). Kim et al., also teach that E42 and K89 of wild-type human IL-18 (i.e. SEQ ID NO: 1) are critical amino acid residues for the integrity of IL-18 structure and are important for binding to cell surface receptors, for signal transduction, and for neutralization by IL-18BP (p. 10998, abstract). The binding of wild-type IL-18 and its various mutants was evaluated by competition assays (p. 10998, abstract and p. 11000, column 1).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Burton et al., with the teachings of Janson et al., and Cox et al., because Burton et al., teach that IL-18 derivatives can be conjugated with polymer moieties, Janson et al., teach the crystal structure of IL-18 with cysteine-38 and cysteine-68 as being solvent accessible, and Cox et al., teach cysteine-reactive PEG moieties of various sizes. Further, Kim et al., teach that E42 and K89 of wild-type human IL-18 (i.e. SEQ ID NO: 1) are critical amino acid residues for IL-18 neutralization by IL-18BP. Attaching a large PEG or mPEG moiety near E42 or K89 would sterically interfere with IL-18BP binding. Reduction in binding of IL-18 could easily be tested with competition assays, as taught by Kim et al. The person of ordinary skill would have reasonably expected success because Burton et al., teach improved pharmacokinetics and subcutaneous bioavailability in proteins, including IL-18, that are conjugated to water-soluble polymers. Because Kim et al., teach that E42 and K89 of wild-type IL-18 are critical to IL-18BP binding, any steric interference with the ability of IL-18BP to bind, near E42 and/or K89 will result in reduced IL-18BP.

Conclusion

SEQ ID NO: 8 is free of the art.

Claims 9-20, 29, 37-38, 42, 45, and 47 are allowable.

Claims 1, 22, 36, 4, 44, and 46 remain rejected.

Claims 6 and 40 are objected to.

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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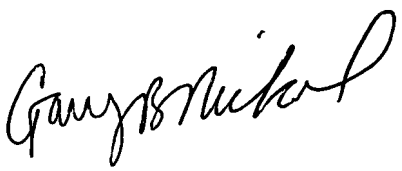

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